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Is There Potential for Granulocyte or Granulocyte–Macrophage Colony Stimulating Factors in Radiotherapy?

P. Janssens, C. Mitine, M. Beauduin and P. Scalliet

The purpose of this communication was to explore which situations in radiotherapy might benefit from concomitant administration of haematopoietic growth factors (HGF). Only large-field radiotherapy is likely to induce bone marrow depression, such as irradiation of Hodgkin's disease. Therefore, we studied 122 patients irradiated for Hodgkin's disease, looking at peripheral blood cell count before, during and after the treatment. One hundred and four treatments were preceded by chemotherapy (MOPP and/or ABVD) and the radiation dose was between 36 and 44 Gy in 2 Gy per fraction sessions. Severe leucopenia (grade III WHO) was very uncommon and justified treatment interruption only twice. In both cases, it was paired with thrombocytopenia. No infection developed. It is concluded that when radiotherapy is used alone, prophylactic use of HGFs does not seem justified. This, of course, does not apply to radiochemotherapy combinations, although thorough investigations in this field are still awaited.

Key words: growth factors, Hodgkin's disease, radiotherapy
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INTRODUCTION

GRANULOCYTE AND granulocyte–macrophage colony stimulating factors (G-CSF and GM-CSF, further referred in the text as haematopoietic growth factors, HGFs) have recently become commercially available. Their ability to improve tolerance to cytotoxic chemotherapy, so that preplanned drug dosages can be delivered without excessive haematological toxicity, has been perceived as a major improvement in haematology and oncology. Moreover, antibiotics and/or hospitalisation needs, resulting from neutropenia-related infections, seem to be reduced, a fact of great importance in European countries where hospitalisation is very expensive [1].

HGFs, however, are very expensive products themselves. A typical filgrastim (Neupogen®) treatment costs between 1500 and 2000 ECU in Belgium. There has thus been great concern about the potential impact of an unlimited use of HGFs on public health budgets, since cancer is a widespread disease and chemotherapy a widespread treatment of cancer. In particular, health care administrations fear that the global impact on health budgets of an unrestricted use of HGF might far outweigh the savings which its use is supposed to bring. Belgian authorities

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have, therefore, severely restricted the indications of HGFs by establishing stringent rules of reimbursement (*Official Journal of the Belgian Government*, 25 August 1992).

It is in this context that the question is raised as to whether the use of HGFs might also be beneficial to patients treated with ionising radiations. The effectiveness of HGFs in radiation-induced bone marrow depression has already been demonstrated [2]. HGF treatment during radiotherapy (RT) does not seem to modify the extrahaematopoietic normal tissue tolerance [3,4]. The currently available molecules (G-CSF, GM-CSF) have no influence on red blood cell or thrombocyte production.

RT-related moderate leucopenia is not infrequent but almost always due to lymphocytic depletion, which mostly results from lymphocyte exposure in blood circulating in the radiation fields [5]. Because granulocytes are mature cells with no clonogenic function, they are insensitive to the usual radiation dose levels (typically 2 Gy per day). It is only at the progenitor level, i.e. upstream in the bone marrow, that granulocytic depletion may be due to RT.

The bone marrow, however, is an adaptative tissue able to multiply its own cell output several times in case of increased cell consumption. In fact, only two types of irradiations may induce severe, potentially hazardous, neutropenia: (1) total body irradiation (TBI) in which 100% of the bone marrow is irradiated at an ablative dose. The neutropenia cannot be taken as a side-effect, since aplasia is actually the goal of the treatment. HGFs are increasingly used after TBI, but as part of a complex strategy in which radiations are only one of many other concomittant myelotoxic attacks. (2) Large-field irradiations, including appreciable proportions of the bone marrow, especially in patients simultaneously treated with other myelotoxic modalities. A good model is the treatment of Hodgkin's disease with total lymphoid irradiation (TLI). In Hodgkin's disease, chemotherapy is frequently given before RT so that the level of haematopoietic stem cells is already decreased when irradiation begins.

Potential indications for HGF therapy in radiation therapy would include severe neutropenia requiring treatment interruption which, in turn, might leave time for the tumour to repopulate, possibly jeopardising the chance of cure [6, 7].

We, therefore, reviewed the history of 122 patients treated for Hodgkin's disease, looking particularly at cases of severe neutropenia which required treatment interruption, and which might have been indications for HGF therapy. We also tried to determine if some predictors could be found which would indicate which patients might benefit from a HGF prophylactic treatment.

MATERIALS AND METHODS

The history of 122 patients treated at Middelheim and Jolimont hospitals between January 1985 and December 1990 was retrospectively analysed. This represents the total number of patients irradiated for Hodgkin's disease at both institutions. The following information was collected: sex, age, disease stage (using the Ann Arbor classification), total radiation dose, total treatment time, previous chemotherapy, white blood cell count at the start and at the end of RT, thrombocyte count at the start and at the end of RT, and unplanned interruptions in RT.

The mean age was 35.2 years (range 7–80). One hundred and thirty-two treatments were carried out since 10 patients received both supra- and infradiaphragmatic RT. One hundred and seven treatments were mantle field irradiation, 14 infradiaphragmatic fields — of whom four inverted Y only and 10 were combined with the mantle field—and 11 involved fields only (supradiaphragmatic). One hundred and four treatments were combined with previous chemotherapy (CT) (MOPP and/or ABVD) and 28 were not. Concomittant CT was not given. The planned radiation dose was 36–40 Gy for large fields; bulky mediastinal masses were boosted up to 44 Gy. All patients were treated with megavoltage energy, 1.8–2 Gy per day, 5 days per week. Blood cell count was measured once a week, and radiotherapy was stopped when the white blood cell count (WBC) fell under 2000 per ml and/or thrombocytes below 100 000 per ml unless this occurred during the few last treatment sessions.

RESULTS

In 86 of the 132 treatments (65%), the difference between the white blood cell count before and after RT, i.e. the differential WBC (DWBC), was negative and larger than 100 WBC per ml. In the 46 remaining treatments (35%), however, the DWBC was positive, i.e. WBC increased during irradiation, essentially because patients recovered from previous chemotherapy during RT (mantle field in all cases); 26/132 treatments resulted in WBC below 3000 per ml, but only three of these 26 dropped below 2000 per ml during irradiation.

As to thrombocytaemia, there was a trend for thrombocyte count (TC) to increase in about 20% of treatments, whether the patient had received previous CT or not. Severe thrombopenia was never a problem; 39/132 treatments resulted in TC below 150 000 per ml with 7 of these 39 below 100 000. The TC never dropped below 50 000 per ml.

Of the three treatments with WBC < 2000 per ml, two also had TC $< 100\,00$ per ml. The third had a normal TC count. Of the 23 treatments resulting in 2000 per ml $<$ WBC < 3000 per ml, four had TC $< 100\,000$ per ml, and another two had 100 000 per ml $<$ TC $< 150\,000$ per ml. There was only one isolated thrombocytopenia in a patient which never recovered, and eventually died from *Legionella* infection.

Treatment interruptions occurred in 18 treatments, of which only two were due to haematological intolerance.

(1) The first patient had a stage IIIA disease with cervical and mediastinal nodes and a positive spleen. Radiotherapy was stopped after 16.2 Gy on an inverted Y, 6 weeks after 40 Gy on a mantle field and four MOPP/ABVD cycles. WBC and TC counts were 3500 per ml and 318 000 per ml before RT and 1200 per ml and 69 000 per ml at 16.2 Gy, respectively. His tolerance to the previous CT or mantle field RT was unremarkable (WBC 3400 per ml and TC 186 000 per ml at the end of the mantle field). A bone biopsy excluded a bone marrow relapse but he only recovered a normal peripheral blood count after 1 year, i.e. rather slowly. He has been well since 1988.

(2) The second patient had a stage IIIA supradiaphragmatic disease with mediastinal mass. She was stopped after 28 Gy on an inverted Y started 3 weeks after 44 Gy on a mantle field without prior CT. WBC and TC counts were 4400 per ml and 377 000 per ml before RT and 1800 per ml and 95 000 per ml at 28 Gy, respectively. Her tolerance to the previous mantle field RT was unremarkable (WBC 4900 per ml and TC 367 000 per ml at the end of the mantle field). Her bone biopsy was negative for tumour invasion and she quickly recovered a normal peripheral blood count (1.5 months). She has been well since 1985.

Febrile episodes were reported in neither patient and hospitalisation was unnecessary. HGFs could have helped both in resuming their inverted Y irradiation, although, retrospectively,

they would not have had much benefit because neither developed infection and both remain in prolonged remission. In addition, HGF therapy would only have corrected the leucopenia, whereas both had an associated thrombopenia.

In addition to these 2 patients, 5 others treated by TLI ended RT with 2000 per ml < WBC < 3000 per ml.

The remaining 16 interruptions were planned to allow for a mediastinal mass regression after 30–40 Gy on a mantle field, before boosting the mediastinum with shrinking fields. These interruptions might have improved the haematological tolerance in these patients, although none had evidence of marrow depression at the time of the interruption.

Looking at the whole series, several factors were investigated as possible predictors for a decreased haematological tolerance to RT.

Previous CT — MOPP and/or ABVD, usually four to six courses — had no clear influence on haematological tolerance with a not inconsiderable number of patients even *recovering* a normal peripheral blood count during mantle field irradiation.

Neither age nor sex had any influence on haematological tolerance in this series. Mean age was 36.4 versus 34.8 years for patients ending RT with less or more than 3000 per ml WBC, respectively.

7/10 patients treated on both sides of the diaphragm (TLI) had WBC < 3000 per ml compared with 22/107 treated with mantle field and 4/14 with an inverted Y only. Only 2/122 patients experienced a WBC drop below 2000 per ml and they had been treated with TLI, mantle first followed by inverted Y. Leucopenia developed in both during the infradiaphragmatic irradiation. The low frequency of leucopenia in patients treated with mantle field coincides with the predominant distribution of active bone marrow in the lower half of the body in adults (25% of bone marrow in the mantle field versus 40% in the inverted Y).

DISCUSSION

Because tumour proliferation does not stop during radiotherapy, the absolute number of cancer cells steadily increases *during* overall treatment time. Treatment interruption or prolongation may thus decrease the chance for cure as the balance between cancer cell production and destruction might bend in favour of the tumour [6,7].

In this series of patients irradiated for Hodgkin's disease, 16 treatments were interrupted for non-haematological reasons and 2 for haematological relative intolerance, both in patients treated on both sides of the diaphragm. This amounts to about 20% of the TLI, which is in accordance with the literature [8,9].

If HGF prophylaxis were to be developed in TLI, it would only benefit 20% of the patients and be wasted in the remaining 80%. Unfortunately, none of the variables analysed in the present series — age, sex, previous chemotherapy, type of chemotherapy, tolerance to chemotherapy — could help identify a subgroup for which prophylaxis could be preferentially targeted.

What impact on treatment tolerance and efficacy do irradiation interruptions due to leucopenia have? This question involves two different aspects. First, the leucopenia which motivates the treatment interruption may expose the patient to the risk of developing a severe infection. Such a complication, however, has not been observed, either in our series or in other reports in the literature [8, 9]. Second, a treatment interruption may give the tumour an opportunity to repopulate during the interval. A repopulation rate requiring a compensation of about 0.3 Gy per day of treatment interruption has been estimated for Hodgkin's disease [6], i.e. something which would easily be compensated for by adding a few fractions whenever necessary — about one fraction of 2 Gy per week — or by accelerating the treatment after the interruption.

Further, the currently available HGFs have no effect on the other bone marrow cell lineage and, particularly, on thrombopoiesis, so that a radiation-induced bone marrow depression with combined cytopenia, cannot be fully corrected by the use of HGFs.

Last but not least, the use of HGFs during a treatment with radiation adds 1500–2000 ECU to the total cost of the treatment — radiotherapy alone costs on average 3000 ECU in Europe — which inevitably raises the question of the cost-effectiveness of such an association. With respect to Hodgkin's disease, a systematic use of HGFs would be clearly counterproductive, i.e. a waste of resources, since the majority of patients do not need it. Even restricted to those few patients which actually develop leucopenia, adding HGFs would not be cost-effective since leucopenia is seldom associated with severe infections, short interruptions can be compensated for by appropriate alterations in the treatment schedule, and only leucopenia but not thrombocytopenia would be corrected.

The high cost of recombinant G-CSF, perhaps justified by the level of investments required for its development, production and testing before it could be commercialised, also raises concern about a possible further cost inflation of chemotherapy, especially in palliative indications. Indeed, the first paper on the clinical use of recombinant G-CSF appearing in the *New England Journal of Medicine* dealt with palliative chemotherapy in patients with overt metastatic disease from urothelial cancers [1]. A comprehensive cost-effectiveness analysis is not available, but some authors cast doubts about the necessity to use G-CSF systematically instead of using it when required by a fever-associated neutropenia [10].

The Belgian authorities follow such advice and accept treatment with G-CSF only if at least one episode of fever-associated neutropenia (or a nadir of at least 5 days with less than 500 per ml WBC) has been documented, and this in a strictly selected number of tumours in which chemotherapy plays a curative role.

Palliation is also an important endpoint, with respect to quality of life but its cost needs to be acurately matched with expected benefits, since life prolongation at all costs can no longer be the common therapeutic approach of oncologists. Despite the reluctance of many clinicians and the important ethical problems raised by preferential allocation of resources in selected situations, we will not escape the need for increasing integration of economics to oncological research.

This is not an era of shrinking resources but one of expanding opportunities for spending those resources. How to allocate them is the most important problem before us. The problem created by technology must be solved by ethics.

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Neoadjuvant Versus Adjuvant Chemotherapy in Premenopausal Patients With Tumours Considered Too Large for Breast Conserving Surgery: Preliminary Results of a Randomised Trial: S6

S.M. Scholl, A. Fourquet, B. Asselain, J.Y. Pierga, J.R. Vilcoq, J.C. Durand, T. Dorval, T. Palangié, M. Jouve, P. Beuzeboc, E. Garcio-Giralt, R.J. Salmon, A. de la Rochefordière, F. Campana and P. Pouillart

The aim of this study was to assess a potential advantage in survival by neoadjuvant as compared to adjuvant chemotherapy. 414 premenopausal patients with T2-T3 N0-N1 M0 breast cancer were randomised to receive either four cycles of neoadjuvant chemotherapy (cyclophosphamide, doxorubicin, 5-fluorouracil), followed by local-regional treatment (group I) or four cycles of adjuvant chemotherapy after primary irradiation ± surgery (group II). Surgery was limited to those patients with a persisting mass after irradiation, and aimed to be as conservative as possible. 390 patients were evaluable. With a median follow-up of 54 months, we observed a statistically significant difference ($P = 0.039$) in survival in favour of the neoadjuvant chemotherapy group. A similar trend was seen when the time to metastatic recurrence was evaluated ($P = 0.09$). At this stage, no difference in disease-free interval or local recurrence between these two groups could be observed. The mean total dose of chemotherapy administered was similar in both groups. On average, group I had more intensive chemotherapy regimes (doxorubicin $P = 0.02$) but fewer treatment courses ($P = 0.008$) as compared to the treated patients in group II. Haematological tolerance was reduced when chemotherapy succeeded to exclusive irradiation. Breast conservation was identical for both groups at the end of primary treatment (82 and 77% for groups I and II, respectively). Of the 191 evaluable patients in the neoadjuvant treatment arm, 65% had an objective response (>50% regression) following four cycles of chemotherapy. The objective response rate to primary irradiation (55 Gy) was 85%. Improved survival figures in the neoadjuvant treatment arm could be the result of the early initiation of chemotherapy, but we cannot exclude that this difference might be attributable to a slightly more aggressive treatment. So far, the trend in favour of decreased metastases was not statistically significant. The local control appeared similar in both subgroups.
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INTRODUCTION

LIMITED INFORMATION exists to support timing decisions in treating human neoplasms. In animal models, survival is optimised when systemic chemotherapy precedes the surgical resection of transplantable tumours, and better results are achieved with a shorter time interval between tumour implantation and start of therapy [1–9].

In pilot studies, locally advanced breast tumours have been shown to regress following pre-operative chemotherapy [10–13], and a complete pathological response could be achieved in 36%